NEW YORK HEART ASSOCIATION

PART I—ABSTRACTS OF PAPERS PRESENTED AT THE SCIENTIFIC SESSION ON RESEARCH, HELD AT THE NEW YORK ACADEMY OF MEDICINE, APRIL 13, 1967

Micropuncture Study of the Effect of Partial Renal Venous Occlusion on Proximal Tubular Fluid Reabsorption in the Nephron of the Rat

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During partial renal venous occlusion, mean peritubular capillary pressure rose from 12 to 25 and proximal tubular pressure from 12 to 23 mm. Hg. The total glomerular filtration rate (clearance of inulin) decreased from 8.7 ± 0.4 (S.E.) to 4.8 ± 0.9 ml./min./kg. Individual nephron GFR diminished from 29.5 ± 2.0 to 16.8 ± 1.5 mμl./min. Tf/P inulin at the end of the proximal convolution was 1.95 ± 0.06 before and 1.78 ± 0.06 during clamping, a statistically insignificant decrease. During control observations, absolute fluid reabsorption varied directly with the square of the tubular luminal radius (r^2) ($p<0.001$) and GFR ($p<0.01$): and fractional reabsorption with passage time ($p<0.001$). During clamping the relation between absolute reabsorption and r^2 was lost, but balance between absolute reabsorption and GFR was sustained ($p<0.001$). The proportionality between passage time and fractional reabsorption was altered (slope decreased) when passage time exceeded 16 seconds during clamping. These data suggest that a factor other than or in addition to tubular volume and passage time is operative to mediate the proportionality between glomerular filtration and tubular reabsorption. *(Supported in part by the New York Heart Association, National Science Foundation, American Heart Association, Life Insurance Medical Research Fund, and Health Research Council of the City of New York.)*

*Human Platelet Glycogenolysis and Glycolysis During Simulated Thrombus Initiation**

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Platelet agglutination and possibly contraction are required for the initiation of thrombus formation. Maintenance of ATP levels is associated with this requirement. Since the metabolic energy of platelets is primarily obtained from glycolysis, various glycogenolytic and glycolytic parameters were investigated. Washed human platelets

were incubated in a modified human Ringer's solution, *p*H 7.1, at 37° for 1 hour. Agglutination and contraction of platelets were achieved by the addition of ADP, thrombin or epinephrine.

In the presence of glucose, glycogenolysis was found to be a potent glycolytic pathway contributing 40% of the lactate produced. The breakdown of glycogen progressed with decreasing rate over a 1-hour period to 43% of initial glycogen levels. Of the glycogen depleted, 53% was converted to lactate, with the theoretical generation of 31 μmoles of ATP per ml. of packed platelets. With glucose present, glycogen breakdown was spared by 13%, with 51% of the glucose uptake converted to lactate. Total theoretical ATP generated was 52 μmoles/ml. Thus only 50% of glucose or glycogen was utilized for glycolytic generation of ATP. Platelet ATP levels declined from 2.70 to 1.94 μmoles/ml. at the end of one hour in the presence or absence of glucose. Despite an increase of 21 μmoles/ml. ATP, maintenance of steady state levels was not attained. This suggests compartmentation of energy requirements.

In the absence of glucose, ADP agglutination increased lactate production 15% (3.3 μmoles/ml./hr.) and glycogenolysis 26% (5.2 μmoles/ml./hr.) over basal levels. Both thrombin and epinephrine increased lactate production 37% and glycogenolysis 48%. A minimal sparing effect on glycogenolysis was noted in the presence of glucose.

Platelets were found to contain interconvertible forms of "active" phosphorylase *a* and "inactive" phosphorylase *b*. Phosphorylase *b* was activated by AMP. Resting level of phosphorylase *a* was 45% of total phosphorylase activity at the beginning and end of one hour of incubation with epinephrine. Increased glycogenolysis could not be correlated with changes in "active" phosphorylase *a*. *(Supported by USPHS FR 5399-05.)*

*Biphasic Effects of Procainamide on Cardiac Conduction**

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Reduction of diastolic membrane potential in automatic (latent pacemaker) cells of the His-Purkinje system resulting from spontaneous phase 4 depolarization has been shown to cause disturbances of conduction and excitability ranging from simple slowing to complete block and inexcitability. Such changes may be a factor in development of reentry. Agents that suppress phase 4 depolarization and restore diastolic potential toward normal should therefore reverse these abnormalities. Thus, contrary to current belief that standard antiarrhythmic drugs, e.g., procainamide, exert solely depressant effects on cardiac conduction, such agents, by virtue of their ability to suppress phase 4 depolarization, may be expected to reverse conduction disturbances due to this cause.

This possibility was tested in isolated strands of canine Purkinje fibers. Transmembrane potentials were recorded simultaneously at both ends of the preparation. Development of conduction disturbances due to enhanced phase 4 depolarization was induced by low rates of stimulation in conjunction with either stretch, hypoxia or reduction of extracellular potassium concentration.

Low concentrations of procainamide (10-30 mg./l.), suppressed phase 4 depolarization, restored diastolic membrane potential toward normal and improved conduction. Higher concentrations (60-120 mg./l.) not only did not improve conduction but usually further increased the conduction dis-

turbance. Presumably, at high concentrations of drug, the beneficial effects of suppression of phase 4 depolarization were outweighed by depressant effects on membrane responsiveness and reduction of maximum diastolic membrane potential. Often such high concentrations actually enhanced automaticity, thus contributing to the further deterioration of conduction that occurred in these instances.

Thus, in instances of conduction disturbances due to phase 4 depolarization of automatic cells, procainamide exerts a biphasic dose-related effect on conduction. Although high concentrations produce the expected depressant effects, low concentrations tend to improve conduction by suppressing phase 4 depolarization. If, as it seems reasonable to suppose, enhanced phase depolarization is a significant cause of conduction disturbances and reentry in the human heart, particularly the diseased human heart, then the action of procainamide in suppressing diastolic depolarization may be an important factor in its antiarrhythmic action in man. *(Supported in part by a grant from Life Insurance Medical Research Fund.)*

Hemodynamics of Paired Electrical Stimulation in Complete Heart Block in Man

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Paired electrical stimulation (PES) was performed in eight adult patients who had complete heart block not associated with acute myocardial infarction. None of the patients was in clinical congestive heart failure nor were they taking digitalis or diuretics at the time of study.

Pressure pulses, maximal rate of rise of pressure (dP/dT) in the pulmonary artery, right ventricle and brachial artery, and cardiac output were measured during the control idioventricular rhythm, during single (SES) and paired (PES) electrical stimulation, and during the administration of isoproterenol.

Satisfactory PES was technically impossible in three patients because of a prolonged absolute refractory period. However, two of these demonstrated a significant increase in dP/dT. The cardiac output fell in all, and one experienced angina with paired pacing.

Of the five patients in whom adequate PES could be performed, only two demonstrated an increased cardiac output despite the fact that four had a significant increase in brachial artery dP/dT. With SES, cardiac output increased above control level in four of seven patients.

Isoproterenol administered as a continuous intravenous infusion in doses of 1 to 16 micrograms per minute for 15 minutes produced a greater cardiac output and brachial artery dP/dT than any of the other interventions in all except one patient, in whom these were maximal with PES. *(Supported by a NYHA Fellowship and USPHS Grant HE-5650-03.)*

Mechanisms of Experimental Atelectasis in Dogs

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The subnormal arterial O_2 tensions observed in patients undergoing anesthesia, chest strapping, and respirator breathing have been attributed to diffuse atelectasis. Atelectasis is thought to result either from obstruction of the airway followed by gradual loss of alveolar volume as gas is absorbed, or from abrupt alveolar collapse when alveolar volume is reduced below a critical level. To evaluate these possibilities, diffuse atelectasis produced by negative-pressure breathing was studied in dogs. Divergence of results among three methods of measuring pulmonary arteriovenous shunt-flow was used to assess the state of inflation of alveoli becoming atelectatic. The methods utilized were measurement of venous admixture, continuous infusion of ^{85}Kr, and rapid injection of ^{85}Kr dissolved in T-1824 dye.

These methods were tested in dogs with occlusion of lobar bronchi since the state of alveolar inflation was known. In dogs breathing air before occlusion the lobes remained inflated for several hours whereas in dogs breathing 100% O_2 the obstructed lobes rapidly became gas-free. The ^{85}Kr infusion and venous admixture techniques measured perfusion of all nonventilated alveoli equally well, whereas the ^{85}Kr-dye method measured only perfusion of gasless alveoli.

The latter method was shown to be influenced by the size of the extravascular space by analyzing simultaneous arterial concentration curves of ^{85}Kr and dye. The mean transit time for ^{85}Kr through airless lung exceeded that for dye, indicating that the isotope diffused from the blood into lung tissue and water. The consequent reduction in early recovery of ^{85}Kr. lowered this estimate of shunt-flow.

In negative-pressure atelectasis, ^{85}Kr infusion and venous admixture estimates again agreed closely; the ^{85}Kr-dye values were 1/5 lower, but in contrast to lobar occlusion studies were the same whether the animals breathed air or O_2. This latter finding suggests that atelectasis caused by negative-pressure breathing results primarily from abrupt alveolar collapse rather than from obstruction of the airway. *(Supported in part by USPHS Grants HE-02001 and HE-05741.)*

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The Mechanical Auxiliary Ventricle: Recent Modifications

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Recent modifications relating to the mechanical auxiliary ventricle and their effects on 63 dogs are presented here. The modifications were:

1) One-piece outer housing of resin-coated fiber glass covered with silicone rubber, in which a flexible inner sac is placed, was used. This housing is thin, light and rigid, and remains uniform during fabrication.

2) Small transducers of various types were imbedded in the auxiliary ventricle to monitor its function and that of the left ventricle.

3) Instead of a constant flow of air, a constant air pressure of 200 to 250 mm. Hg was applied, synchronized with the natural heart by means of a dual beam oscilloscope. One beam is triggered by either the left ventricular pressure curve or the ECG, and the other can be adjusted to the time delay required for the function of the unit.

4) The aortic arch was cut instead of being ligated between the two anastomoses, so that all the blood passes through the auxiliary ventricle. This reduces the risk of clotting and kinking of the limbs.

In short-term hemodynamic studies in 19 dogs, with the auxiliary ventricle functioning up to 12 hours, left ventricular peak pressure was reduced as much as 80 mm. Hg (46% of the initial pressure); the systolic area of the left ventricular curve was reduced 58%; and the duration of systole by 50 msec.

In long-term experiments in 44 dogs in which intermittent pumping was employed, 30 survived the implantation, 9 surviving 1 month. The longest survival was 9 months. Thromboembolism was a complication in some long-term survivors.

Strain-gauge type transducers appeared most promising, being selective of aortic pressure and aortic valve sound and unaffected by noise from the solenoid valve used to control the compressed air.

Cineangiograms were used to analyze the function of the unit. *(This work was supported by USPHS Grant HE-06510.)*

Localization of Subcellular Sites of Sodium and Calcium Ion in Mammalian Myocardium

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The localization of the subcellular site of calcium sequestration and of sodium and calcium competition in mammalian cardiac muscle was undertaken in an electron microscope study of 42 canine papillary muscles. By means of a recently developed technique, muscles were cannulated through an intact arterial supply, and were isolated and perfused with a solution of the desired tonicity and ionic composition while function was monitored. At the end of the experiment, iced glutaraldehyde replaced the perfusate and the tissue, having been fixed instantaneously through its own vasculature, was processed for examination in the electron microscope.

Five control muscles were perfused with oxygenated isotonic solution containing NaCl 130mM, $CaCl_2$ 5mM, KCl 4mM, $MgCl_2.6H_2O$ lmM, NaHPO4.H_2O 0.435mM, $NaHCO_3$ 14 mM, and glucose 5.56mM. These muscles showed good function and excellent preservation of ultrastructure.

In 11 muscles, a 75% reduction of sodium in the perfusate produced an increase in systolic tension and resulted in dilation of the sarcoplasmic reticular tubules. A 3- to 5-fold increase in perfusate calcium in three muscles produced exactly the same phenomenon.

In a second series of experiments, 20 muscles were preserved with osmic acid in a buffered solution of potassium antimonate at the end of each perfusion. This resulted in the sharp localization of an electron-dense, granular precipitate, tentatively identified as calcium antimonate, in the lateral sacs of the sarcoplasmic reticulum and along the I band of muscle sarcomeres.

These observations correlate with the proposition that the sarcoplasmic reticulum in mammalian cardiac muscle has a special ability to sequester or release calcium ion. As such, it may function as the link between excitation and contraction, facilitate muscle relaxation, and control the degree of muscle inotropism. *(Supported by grants G 64-3 from the Life Insurance Medical Research Fund and USPHS HE 05741—05.)*

NEW YORK HEART ASSOCIATION

PART II—ABSTRACTS OF PAPERS SUBMITTED FOR PRESENTATION AT THE SCIENTIFIC SESSION ON RESEARCH, HELD AT THE NEW YORK ACADEMY OF MEDICINE, APRIL 13, 1967

Structure-Activity Relations of Synthetic Vasopressin and Oxytocin Hormones in the Microcirculation: A Cellular and Molecular Basis for Shock Therapy

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The synthesis of vasopressin has led to the preparation of a number of analogues of the naturally occurring hormone that while still maintaining marked vasoconstrictor activity exert reduced or virtually negligible effects on the kidneys. One such analogue, PLV-2 or 2-phenylalanine-8-lysine vasopressin, has been reported by our group to increase survival of rats and rabbits subjected to hemorrhage, intestinal ischemia shock, and traumatic shock. On direct microscopic observation of the mesenteric microcirculation in rats and rabbits subjected to hemorrhage and to the shock of intestinal ischemia, we found that PLV-2 maintained arteriolar and venular tone, sustained vasomotion, and decreased the abnormally high reactivity to topically applied epinephrine that is characteristic of shock. The net influence of these *selective* microvascular effects of PLV-2 was to improve true capillary inflow, distribution, and outflow. In view of these observations in the shocked animals, a systematic study is currently under way in our laboratory to determine whether the pharmacologic effects and sites of action of these neurohypophyseal peptides in the microcirculation undergo change as their chemical structures are modified. These studies are being done in the hope of being able to suggest synthesis of vasotropic compounds that may be more highly effective in shock. Microvascular smooth muscle actions currently are being studied *in vivo* on the rat mesoappendix preparation. Topical application of Pitressin, 8-arginine vasopressin, 8-lysine vasopressin, and PLV-2 to the mesoappendix of the rat produces in dose-dependent fashion a venular to arteriolar gradient of constriction in the microcirculation—the reverse of epinephrine, norepinephrine, or electrical stimuli. Local application of 8-ornithine vasopressin, oxytocin, or 2-phenylalanine-8-ornithine oxytocin to the mesoappendix of the rat produces in dose-dependent fashion a constriction of precapillary sphincters, followed by metarterioles, then venules and, lastly, by arterioles as the doses of the three analogues are increased. Our observations thus far indicate that vasopressins and oxytocins exhibit *selective* microvascular effects. At least two distinct types of gradients of reactivity appear to exist for these peptides in the microcirculation. A particular type of gradient of responsiveness may depend on the basicity as well as length of the side chain of the amino acid moiety in position 8. *(Supported in part by USPHS Grants HE 09042 and HE 11391.)*

Effects of Diphenylhydantoin on Mammalian Heart Muscle

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Recent studies have demonstrated that diphenylhydantoin (DPH) consistently reverses human and experimentally induced canine arrhythmias but may depress cardiovascular performance. The present experiments evaluated the direct effects of antiarrhythmic concentrations of DPH on the contractility of isolated cardiac muscle.

Cat papillary muscles and trabeculae carneae (4-8 mm. by $<$ 1 mm.) were field stimulated 30 to 60 times/min. at 30° and 37° C. Isometric contractions were recorded from muscles at fixed length, at the peak of the length-tension curve or on the descending (failing) limb. Isometric tension was recorded from muscles undergoing smooth programmed changes in length. Force-velocity relations were obtained from isotonic recordings.

Addition of DPH (10^{-9} to 10^{-6} *M*) had insignificant inotropic effects on the maximum rate of isometric force development, peak systolic force, and diastolic compliance in normal and overstretched muscles at fixed length. Similar results were observed over the entire length-tension curve in muscles undergoing programmed length changes; DPH had no effect on the hysteresis displayed by such muscles. Maximum rate of isotonic shortening was minimally effected. DPH diluent, in quantities necessary for dissolving DPH, had substantially no effect on contractility.

DPH (10^{-8} to 10^{-6} *M*) had negligible effects on increased contractility observed during administration of isoproterenol (10^{-7} *M*) or increased calcium.

In addition, the effects of DPH were tested on the facilitation of Ca^{45} transfer from aqueous to organic phases caused by lipids extracted from canine microsomes. The negative inotropic effect of other antiarrhythmic substances has been related to inhibition of such transfer. DPH (10^{-8} to 10^{-6} *M*) caused inhibition quantitatively similar to that reported for beta adrenergic blocking agents and quinidine.

Results indicate that DPH, in the concentrations used, has little or no direct negative inotropic action on cardiac muscle and suggests that depressant effects seen with the intact circulation may arise peripherally. *(Supported by USPHS Research Grant HE-08508 and a grant from Parke, Davis & Co.)*

Hemodynamics of High-Inflow Portal Hypertension

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Intensive hemodynamic investigation of a patient with myeloid metaplasia, massive splenomegaly, and bleeding esophageal varices gives evidence of the existence of a syndrome of high-inflow portal hypertension.

Hepatic function was normal. Inferior vena cava, umbilical vein, and cervical thoracic duct were cannulated. Celiac and superior mesenteric arteriography were per-

formed; subsequently a balloon catheter was passed into the splenic trtery under fluoroscopic control. Pressure, pO_2, pCO_2 and pH of arterial, venous, and lymphatic samples were determined in the resting state, with thoracic duct drainage, with balloon occlusion of the splenic artery, and after deflation of the balloon. Thoracic duct drainage was replaced volumetrically.

Initial thoracic duct oxygen tension was elevated to 86 mm. Hg. Thoracic duct drainage reduced splenic size and lowered umbilical vein pressure from 35 to 27 cm. H_2O without fall in caval pressure. Balloon occlusion of the splenic artery promptly lowered umbilical venous pressure further to 21 cm. H_2O, with concomitant elevation of thoracic duct pressure from 18 to 47 cm. H_2O and appearance of hemorrhagic lymph. Deflation of the balloon was accompanied by prompt return of umbilical venous hypertension to 35 cm. H_2O, fall in thoracic duct pressure to 23 cm., and disappearance of blood from lymph drainage. Arterial and central venous pressures were stable throughout the study.

At operation, occlusion of the splenic artery lowered hepatic vein wedge pressure from 33 to 26 cm. H_2O. One week after splenectomy, hepatic vein wedge pressure was 13 cm. H_2O and pancytopemia reversed.

The effect of occlusion of the splenic artery on umbilical vein and hepatic wedge pressures appears to confirm the existence of high portal inflow and pressure due to increased splenic blood flow. Elevated thoracic duct oxygen tension suggests arteriovenous shunting. Mechanisms for changes in pressure and character of thoracic duct drainage are discussed.

The Role of Norepinephrine Synthesis in Maintenance of Cardiac Catecholamine Content

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Norepinephrine, a natural transmitter, is stored in the dense core of vesicles of sympathetic nerve endings. Small amounts of this amine are released continuously into the circulation in order to maintain tonic activity; increasing amounts are released in response to sympathetic nerve stimulation. In experimental animals (guinea pigs and rats) cardiac catecholamine concentrations remained unaltered even in the presence of vigorous sympathetic activity produced by 1) prolonged sympathetic nerve stimulation; 2) exposure to cold for 6 h.; 3) administration of histamine or β-tetrahydronaphthylamine. Such maintenance of endogenous amine levels was not possible when synthesis of norepinephrine was inhibited by the tyrosine-hydroxylase inhibitor, α-methyltyrosine. In this case tissue catecholamine levels were reduced. This reduction, however, was antagonized by pretreatment with ganglionic blocking agents, adrenergic neurone blocking agents, monoamine oxidase inhibitors, or by destruction of the brain and spinal cord. The usual elevation in catecholamine levels after inhibition of monoamine oxidase or after ganglionic blockade was not observed when synthesis was inhibited by α-methyltyrosine.

The "common factor" in all these experiments is the inhibition of spontaneous release due to "tonic" impulses in sympathetic nerve fibers. This suggests that once synthesis is inhibited, tonic release of catecholamine is sufficient to cause gradual depletion of the amine. This depletion after α-methyltyrosine was increased when sympathetic nerve activity was increased by various procedures. Since α-methyltyrosine did not affect the accumulation of H^3-norepinephrine in the rat heart, these findings suggest that synthesis of catecholamine is

indeed increased in response to increased sympathetic nerve activity, which helps to maintain normal levels of tissue catecholamine. Thus the present study shows that maintenance of endogenous amine levels is based largely on adjustment of local norepinephrine synthesis, which is presumably regulated by activity in the sympathetic nerves. *(Supported in part by a grant from the Council of Tobacco Research—U.S.A.)*

Some Effects of Diphenylhydantoin on Human Atrioventricular Conduction

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Diphenylhydantoin (DPH) is effective in treating cardiac arrhythmia, notably atrial arrhythmias induced by digitalis excess and ventricular arrhythmias. Most effective antiarrhythmic substances may have a significant depressive effect on AV conduction, and this becomes a consideration in their use. The effect of DPH on AV conduction in man was evaluated when the drug was given alone or after parasympathetic (atropine) or sympathetic (propranolol) blocking agents. Subjects with normal and diseased hearts were studied. The heart was paced at a constant rate through a right atrial electrode catheter; a test stimulus was applied every sixth or seventh drive cycle. The interval between the drive and test stimuli was shortened by 5-msec. intervals and absolute and functional refractory periods (RP) of the AV conducting system were determined. ECG, stimulus artifacts, and vascular pressures were monitored on a switched-beam oscilloscope.

Results indicate that in patients with either normal or diseased hearts, the AVRP decreased by an average of about 35 msec. after DPH. Variance was found, in a few cases, in the magnitude of change in the absolute compared with the functional AVRP. The acceleration of AV conduction after DPH tended to be greater in patients receiving digitalis. The AVRP returned toward control in parallel with the decline in plasma DPH levels with time.

Although atropine shortened and propranolol lengthened the AVRP, neither abolished the DPH effect; however, the per cent decrease in AVRP after DPH was less after either drug. The mild hypotension induced by DPH was short-lived in comparison to the alterations in AV conduction, making reflex changes an unlikely explanation for the observed acceleration of AV conduction.

It is concluded that, in a therapeutic dose that depresses ventricular automaticity, DPH accelerates AV conduction, at least partly through a direct effect on the AV conducting system. *(Supported by USPHS Grant HE-05941 and a grant-in-aid from Parke, Davis & Co.)*

The Effect of Artificial Pacing on Cardiac Output in Congenital Heart Block

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Underlying heart disease is generally present in acquired heart block and may modify the effect of heart rate on cardiac output. However, in congenital heart block, the hemodynamic effects may be determined only by the slow rate and not by any myocardial factor.

Two patients with isolated congenital heart block whose ages were 6 and 16 years respectively were studied. Measurements of cardiac output by the dye dilution technique were made during complete heart block with a slow ventricular rate and during more rapid heart rates induced by an electrode catheter in the right ventricle. Intracardiac pressures were also recorded. In each instance, there was no increase in cardiac output during more rapid ventricular pacing. An insignificant increase from 2.8 l./min. to 3.0 l./min. was present in the 6-year-old patient, and a decline from 5.4 l./min. to 4.5 l./min. was observed in the other. The initial, resting, high stroke-volume during heart block decreased from 56 cc. to 29 cc. in the first patient and from 136 cc. to 33 cc. in the second, with an increase in rate from 37 to 130 per minute.

The increased stroke volume in these patients with heart block is probably related to a long diastolic filling period, which results in increased myocardial contractility by a healthy myocardium. This accounts for the normal resting cardiac output. In acquired heart block, however, stroke volume may not increase sufficiently, despite the longer diastolic filling period. Therefore the resting cardiac output may be low with slow rates. Under these circumstances, increasing the heart rate by an artificial pacemaker may increase the cardiac output. In isolated congenital heart block, increasing the heart rate alone may not result in an increased cardiac output.

These findings suggest that the only indication for pacemaker therapy in isolated congenital heart block is the occurrence of Adams-Stokes attacks.

Intracavitary Electrocardiographic Double Atrial Activity in the Homotransplanted Puppy Heart

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Since the electrical atrial activity of the transplanted heart is poorly understood, the following investigation was undertaken.

A nine-lead electrocardiogram was recorded under ambient conditions in 30 puppies before and after orthotopic cardiac homotransplantation under profound hypothermia and by a method of continuous suture. Atrial activity was further investigated by esophageal and intracavitary leads. Histocompatibility was evaluated by several biological methods.

Postoperatively, two foci of atrial activity were demonstrated by the intracavitary tracing in all cases. The findings show that the sinus node of the recipient innervates atrial tissue remaining *in situ* and responds to extrinsic neurogenic influence, but is blocked at the suture line and prevented from initiating ventricular contraction.

The findings also show that donor atria usually respond to their own sinus nodes, but occasionally a new atrial pacemaker is found. These impulses are independent of neural influences but provide the stimulus for ventricular contraction.

Rejection affects the atrial activity of the donor by: 1) slowing down the donor sinus node, 2) causing transient sinus arrest that results in ventricular irregularity, and 3) producing permanent nodal rhythm. All such effects are reversible by immunosuppressive therapy except in cases of severe histoincompatibility. *(This work was supported by USPHS Grants HE-06510 and FR-05497.)*

The Effect of Respiratory and Metabolic Acidosis on Myocardial Contractility

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Previous studies have led to conflicting opinions on the effects of *p*H alterations on the myocardium and on peripheral resistance. The isovolumic left ventricle allows the effects of *p*H on the myocardium and the peripheral vasculature to be evaluated separately and permits measurement of myocardial contractility in terms of maximum rate of pressure rise. Experiments were carried out in 6 dogs to study respiratory acidosis and in 7 dogs to study metabolic acidosis produced by administration of lactic acid. Results showed that after 20 minutes of equilibration with a 30% CO_2 to 70% O_2 gas mixture there was no decrease in myocardial contractility if the *p*H was above 7.0. If the *p*H was below 7.0, the dP/dT averaged 47% of control; peripheral resistance averaged 143% of control. On the other hand, 15 minutes following the injection of lactic acid, dP/dT was 73% of control and peripheral resistance was 81% of control. During preparation of all animals, a base deficit developed; when the deficit was corrected with sodium bicarbonate, the dp/dT rose an average of 185% of control. It is concluded, therefore, that acidosis produced by hypercarbia does not depress myocardial contractility unless the *p*H falls below 7.0. Metabolic acidosis or lactic acidemia depresses myocardial contractility and this effect is reversed by $NaHCO_3$. This depression does not appear to be solely a function of the *p*H, but results from metabolic products which usually lead to a depression of the *p*H. *(Supported in part by grants from USPHS and AHA.)*

Ventricular Asystole and the Vagus

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Reflex vagal excitation can lead to sinus arrest but it is not clear why there should also be ventricular asystole. To investigate this point, the right vagus in dogs was stimulated for 2 minutes; the ventricles were driven during the first minute. The period of ventricular asystole was prolonged when the drive rate was faster and was shortened when the drive rate was slower than the control sinus rate. The asystolic period was shortened when the sinus rate was slowed by graded vagal stimulation before maximal vagal stimulation. The period of asystole was prolonged by driving the ventricles at a rate higher than the sinus rate prior to vagal stimulation. In dogs with chronic atrioventricular block, "overdriving" the ventricles led to temporary inhibition of ventricular pacemakers. In dogs with acute atrioventricular block, the coronary sinus plasma potassium level increased in proportion to the increase in ventricular driving rate. These results support the concept that the slowly discharging ventricular pacemakers are inhibited by the higher rate of the atrial pacemakers; this inhibition becomes apparent when the atrial pacemakers are suppressed by the vagus. The mechanism of inhibition may be related to a rate-dependent change in extracellular potassium concentration. *(Supported in part by USPHS and AHA.)*

Effects of Heparin, Protamine, and Low Molecular Weight Dextran (LMD) on Electrokinetic Characteristics of Canine Blood Vessel Intima In Vivo.

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Electrokinetic characteristics of canine blood vessel intima have been determined *in vitro* from streaming potential and electro-osmosis measurements. These experiments confirm that the intima is negatively charged under normal conditions. Injury reduces the negative charge density and may even make the intimal surface positive. For comparison with *in vitro* streaming potential measurements in canine blood vessels, measurements were carried out *in vivo* between two electrodes placed at a known distance apart in both the aorta and femoral arteries. Positive streaming potentials of 0.2 to 0.4 mv. for the aorta and 0.5 mv. for the femoral artery were recorded at resting flow rates. These results are in excellent agreement with corresponding *in vitro* studies using the same distance and flow rates. The second part of the experiments involved determination of the effect of heparin, protamine, and LMD on the electrokinetic

characteristics of the aorta and femoral arteries. Intravenous heparin (2 mg./kg.) increased the streaming potential to 0.7 mv. across the aorta and to 0.8 mv. across the femoral artery. Protamine (2 mg./kg.) caused reversion of the streaming potentials to the original values. Intravenous LMD (10% w/v) behaved similarly to heparin, producing a linear increase in streaming potentials with an increase in the volume of dextran infused. The anticoagulant effects of heparin and LMD are well known. It is very probable that the mechanism of their action is by adsorption on the intimal surface and other thrombogenic proteins in the blood stream, with consequent increase in the negative surface charge density as manifested by an increase in the streaming potential. *(Supported in part by USPHS Grant HE-07371-04, 05.)*

Metabolic Studies with an Acyl Guanidine in Primary and Secondary Hyperaldosteronism

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The effects of a potassium-sparing agent, MK 870, on Na and K balances were investigated in the metabolic ward. Study periods were alternated with recovery periods while dietary intakes of Na and K remained constant. Case No. 1 was one of probable primary hyperaldosteronism—i.e., hypertension, hypokalemia, alkalosis, without renal disease; salt loading produced increased urinary excretion of sodium and potassium without reduction in the greatly increased 24-hour urinary excretion rates of aldosterone. Five days of MK 870 resulted in correction of hypokalemia and alkalosis, while 5 days of 300 mg. aldactone effected only a modest rise in serum K. In 4 cases with refractory edema and hyperaldosteronism, MK 870 was ineffective *per se.* Once an effective diuretic regimen, including ethacrynic acid (EA), was established, striking negative potassium balances were often seen. In all cases when MK 870 was added to the regimen enhanced natruresis, diuresis, but less K loss and decreased systemic alkalosis occurred. In another patient, an edematous cirrhotic, treatment with furosemide produced diuresis, decreased K, increased CO_2, and hepatic precoma. When MK 870 was added to the same regimen, enhanced diuresis and natruresis without significant change in K, CO_2, or mental state were observed. MK 870 appears to be an effective diuretic that reverses the hypokalemia of primary hyperaldosteronism and that reduces the propensity to hypokalemic alkalosis of other diuretic agents in secondary hyperaldosteronism with edema. *(Supported by USPHS (AM 2828) and the American Heart Association.)*

Epicardial Activation of the Hypertrophied Right Ventricle in Man

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The sequence of epicardial activation of the right ventricle has been studied at open heart operation in 9 patients with rheumatic heart disease and mitral stenosis who underwent mitral commissurotomy. Prior to cardiopulmonary bypass, epicardial activation times were obtained from 11 to 22 right ventricular sites and 4 to 20 left ventricular sites by the recording of close bipolar electrograms.

All patients had significant pulmonary hypertension (pulmonary artery pressures ranged from 38/18 to 110/44), and right ventricular enlargement by x-ray criteria and confirmed at operation. None of the patients had right bundle branch block. In all patients, the prepapillary surface of the right ventricle was activated at the normal time (15 to 20 msec. after the onset of the QRS complex). The vectorcardiogram or the electrocardiogram showed right ventricular hypertrophy in 4 patients. These 4 patients had significant delays of the epicardial activation times of the superior aspect of the free wall of the right ventricle and right ventricular outflow tract. The 5 patients who did not show right ventricular hypertrophy on the electrocardiogram or vectorcardiogram had no significant delays in the right ventricular epicardial activation times.

This study suggests that there is good correlation between the vectorcardiographic and electrocardiographic patterns of right ventricular hypertrophy and the epicardial activation sequence of the right ventricle. Right ventricular enlargement delineated by x ray and confirmed at operation may not be demonstrated by the vectorcardiogram or electrocardiogram as long as the epicardial activation times of the right ventricle are within normal range. The appearance of signs of right ventricular hypertrophy on the vectorcardiogram or electrocardiogram appears to be related to the development of delays in activation of the right ventricle. *(Supported by USPHS Grant HE 10583-02.)*

The Role of Histocompatibility in Orthotopic Transplantation of Puppy Hearts

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This study was carried out to determine the role of histocompatibility in puppies with orthotopic heart transplants. Fourteen animals were used, whose donors had been selected on the basis of histocompatibility tests (normal lymphocyte transfer test, irradiated hamster test, and leukoagglutination test). The postoperative course of these puppies was followed carefully with regard to their ECG's, clinical status, and immunosuppressive therapy. The ECG's showed a close correlation between QRS voltages in

lead 2 and the grade of histocompatibility as indicated in the test results, both in the immediate and later postoperative periods.

The immunosuppressive therapy chosen was basically Solu-Medrol, supported with Imuran; Actinomycin C was added during acute rejection crisis. This treatment appeared to be most effective in the group showing average histocompatibility, and although some puppies with poor histocompatibility responded to the therapy, they inevitably died of heart failure shortly afterward. The postoperative clinical coarse of the animals with good compatibility, as regards activity, appetite, growth, and so forth, was much smoother than that of those with poor compatibility; however, the former group generally succumbed as a result of intercurrent infection. Survival times correlated with the degree of compatibility. Postmortem histological findings on the hearts showed equivocal results. *(This work was supported by USPHS Grants HE-06510 and FR-05497.)*

Lidocaine in Ventricular Arrhythmia

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Lidocaine has been advocated in emergency treatment of ventricular arrhythmia, but few objective data are available. Despite enthusiastic clinical application in the treatment of abnormal rhythms the drug has not been approved by the Food and Drug Administration as an antiarrhythmic. Single and multiple doses of lidocaine, 1 to 2 mg./kg., were given intravenously to 26 patients with ventricular premature complexes (VPCs) with continuous ECG monitoring and periodic assay of blood levels. Transient lightheadedness or sleepiness occurred in 62%. Blood pressure, sinus rate, and QRS duration were unchanged. Frequency of VPCs was reduced after lidocaine in all subjects. Lidocaine blood levels 5 minutes after injection of 1.0 mg./kg. varied from 0.3 to 1.8 μg./ml. and were inversely proportional to body weight. Initial antiarrhythmic effects occurred with 0.6 to 1.2 μg./ml. The $t_{1/2}$ of lidocaine in blood approximated 20 minutes. In 53% of subjects, reduction in VPC incidence persisted more than 1 hour. Prolongation of effect could not be correlated with blood level of drug. In 2 patients with supraventricular arrhythmia with A-V block, ventricular rate increased markedly following drug. In unanesthetized trained dogs with surgically induced complete heart block, lidocaine did not affect atrial rate, slowed ventricular rate, and prolonged asystole following abrupt cessation of ventricular driving. Dose response experiments in these dogs show minimal effect with 0.5 mg./kg. and systemic toxicity after 4 mg./kg. The influence of the drug on ventricular automaticity has been correlated with the arterial blood concentration. *(Supported in part by Astra Pharmaceutical Products, Inc.)*

A Comparison of Left Heart Bypass under Hypovolemic and Arfonad Hypotension

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Left heart bypass, a form of myocardial augmentation, has been shown to reduce myocardial oxygen consumption effectively, particularly in a hypotensive model. Previously, hypotension had been produced by hypovolemia, but in an effort to utilize this observation clinically, chemically induced hypotension was employed. Arfonad, a ganglionic blocking agent, was selected because of the few side effects, rapid onset, and short duration of action of this drug.

Pulsatile left heart bypass through the Senning-Dennis cannula (obviating the need for thoracotomy) was performed. Cardiac output and electrocardiographic, aortic, and left ventricular pressure curves were recorded at carefully maintained levels of pressure. Cardiac work was determined by the pressure-time product (PTP), a modification of Sarnoff's tension time index.

The pressure-time products of control studies and assisted studies under Arfonad hypotension were compared at equivalent pressure levels with control and assisted studies obtained under hypovolemic conditions. The pressure-time products of controls (*without* any assistance) under chemically induced hypotension fell an average of 15.8% with each reduction of 25 mm. Hg in mean arterial pressure, compared with a 15.5% reduction with hypovolemia. Arfonad hypotension reduced cardiac output 5.6% and 16.4% at 100 and 75 mm. Hg, respectively. At these same levels, hypovolemia reduced the output by 52% and 58%. At 50 mm. Hg mean arterial pressure, Arfonad produced a 49% reduction while hypovolemia showed a reduction of 64%.

Left heart bypass under Arfonad hypotension reduced the PTP an average of only 2.5% with each 25 mm. Hg decrement in pressure from 150 to 75 mm. Hg while hypovolemia caused the PTP to fall 9.5% with each decrement in pressure.

The difference is striking at 100 and 75 mm. Hg, where the PTP was reduced 18.0% and 20.8% with Arfonad, contrasted with 45.5% and 50.8% in the hypovolemic model.

Altough hypotension produced by hypovolemia increased the efficiency of the left heart bypass system, it is apparent that the hypotension produced by Arfonad does not have a similar effect. *(Supported by State University of New York, USPHS Grants HE 01011-16, and 2R01-HE-07028-05, and AHA Grant 65G-72.)*

Systems Analysis Correction of Dye Dilution Curves

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Distortion is introduced into dye dilution curves by the withdrawal of blood through sampling tubes and densitometric apparatus. Elimination of this distortion would result in the inscription of a curve similar to that obtained with intravascular recording. To measure the error, blood was withdrawn through a cardiac catheter and densitometer. The total system was analyzed by applying a step function input of indocyanine-dyed blood and recording output. The response was shown to be a single exponential of time constant T. By the techniques of system analysis the transfer function of the system was determined by means of Laplace transformations to be $\frac{1/T}{s + 1/T}$. Uncorrected dye curves (Cu) were passed through a compensating electronic network to eliminate system error, and corrected curves (Cc) were recorded. Experiments were performed with a pusatile blood pump with variable ejection fractions. Cc, recorded by withdrawing blood just distal to the "aortic" valve, revealed a more rapid upstroke than Cu and a series of steps on the downslope. The heights of these steps were used for calculation of the residual fraction with excellent results. The system was applied to curves obtained in humans with left ventricular injection and supra-aortic valvular sampling. In subjects without valvular regurgitation, ejection fractions in the range of 0.4 were obtained. *(Supported by a research grant from the Nassau County Heart Association.)*

Coronary Sinus Blood Flow in Counterpulsation

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For counterpulsation to be effective in myocardial failure it appears important that it increase the amount of available oxygen by increasing coronary blood flow (CBF). Although aortic diastolic pressure may increase and cardiac work may decrease, it cannot be assumed that these changes are paralleled by improved myocardial perfusion.

Method: Counterpulsation was applied to 25 dogs. Central aortic and left ventricular pressures, cardiac output, CBF and pO_2 in the coronary sinus and aorta were measured. Left ventricular stroke work (VSW), maximum rate of ventricular pressure ascent (dP/dT), time-tension index (TTI), and myocardial oxygen consumption (MOC) were calculated. Animals in Group 1 were normotensive with systolic pressures above 100 mm. Hg. Group 2 animals were made hypotensive, either by graded hemorrhage or by temporary obstruction of left ventricular outflow. After the effects of counterpulsation were studied, Group 2 animals were made normotensive by transfusion or epinephrine infusion.

Result: In every dog of both groups counterpulsation lowered aortic peak systolic pressure (mean 11%) and end diastolic pressure (mean 13%) and raised mid-diastolic pressure (mean 72%). All parameters of ventricular work decreased with counter-

pulsation by the same amount in both groups; VSW by mean 35%, TTI by mean 30% and dP/dT by mean 20%. However CBF differed between the groups, remaining essentially unaltered in Group 2 and increasing by a mean of 24% in Group 1, a difference paralleled by the change in MOC.

Conclusion: Counterpulsation decreased the work of the myocardium proportionately in normotensive and hypotensive animals. Despite this decreased work the myocardium of the normotensive dog consumed more oxygen when it was made available by an increase in coronary flow. Thus the calculated myocardial work during counterpulsation is not a good measure of the total demand of the myocardium for oxygen. In order to avoid inadequate oxygenation the CBF must be increased even if calculated myocardial work decreases. This was achieved only by maintaining the aortic pressure at normotensive levels. *(Supported by USPHS Grant H-3743, Health Research Council of the City of N.Y. under contract 1-237, and by the Health Research Center Fund.)*

Myocardial Metabolism in Complete Heart Block and Induced Tachycardia

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Coronary blood flow (CBF), cardiac output (CO), myocardial oxygen consumption (MVO_2), arteriovenous lactate and pyruvate differences, myocardial excess lactate (XL), and cardiac work were measured in five patients with complete heart block at idioventricular and "normal" rates and with induced tachycardia. In three patients (Group 1), CO and MVO_2 increased while XL decreased with pacing at a "normal" rate, indicating improved myocardial function. In two (Group 2) the CO failed to rise. Both MVO_2 and XL increased, indicating decreased efficiency and increased anaerobic metabolism.

Electrical pacemaking may elevate MVO_2 and initiate anaerobic metabolism in certain patients; this may explain the occasional onset of heart failure with pacemaking. Induced tachycardia at modest rates produced a decrease in MVO_2 and increase XL in both groups instead of the increase in MVO_2 predicted by the heart rate-blood pressure index of Katz.

These studies indicate that a patient's "optimal" rate is a compromise between rate effects on CO and MVO_2. Pacemaking at "normal" rates may be damaging to certain patients; modest tachycardia was harmful to all patients studied. *(Supported by USPHS Training Grant 5-T01-HE-05686.)*

Group	*Rate*	*CO l./min.*	*CBF ml./min.*	*MVO_2 100g.*	*XL mM*
1	32	3.24	83	11.8	0.40
	77	4.30	196	21.4	0.14
2	52	2.95	122	14.4	0.03
	85	3.02	208	20.9	0.20
1	108	4.80	162	16.2	0.73
2	140	2.62	183	17.6	0.48

Alterations in Peripheral Pressure Pulse Contour During Acute Aortic Insufficiency in Man

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Previous studies of the hemodynamic effect of acute aortic insufficiency have been limited to the experimental animal. The present study will describe our observations of the effect of acute aortic insufficiency in man, transiently produced during diagnostic cardiac catheterization. As part of the diagnostic study a retrograde catheter was passed via the femoral artery by the Seldinger technique. It was noted that the preformed "J"-shaped retrograde catheter was held up momentarily in the region of the aortic valve, just before entrance into the left ventricle. During passage of the retrograde catheter the brachial artery pressure was constantly monitored. The results to be presented clearly demonstrate that aortic regurgitation was produced by the "J"-shaped, looped catheter when it was placed in the region of the aortic valve and permitted hemodynamic studies to be performed.

Twenty-eight consecutive patients who required retrograde catheterization were studied. In eight there was no evidence of aortic regurgitation, even though the catheter was in the area of the aortic valve. In the remaining 20, aortic regurgitation was produced and a diastolic murmur became audible over the base of the heart; this was not present before or after catheterization. In two of these patients the procedure was tolerated poorly; consequently the catheter was then advanced quickly into the left ventricle. The remaining diagnostic studies were completed uneventfully.

Associated with the diastolic murmur there were characteristic alterations in the pressure pulse of the brachial artery. There was a sudden drop in the diastolic and a slight drop in the systolic pressure, with a resultant increase in the pulse pressure. The change in heart rate was very slight. The systolic ascent and the maximum rate of change (dP/dT) of the brachial pressure pulse increased suddenly. The dicrotic wave, which was well defined during the control period, descended to a lower level, became less prominent, and in several patients could not be defined. The systolic and diastolic descent of the pressure pulse was more rapid, resulting in a lower diastolic pressure. There is evidence that the isometric contraction time was shortened and that the ejection time was prolonged during aortic insufficiency. All the alterations described quickly reverted to normal in one or two beats when the catheter was withdrawn. *(Supported by the Rosenberg Toner Heart Fund.)*

The Biphasic Renal Response and Associated Hemodynamic Changes in Patients Receiving Chlorpromazine Intravenously

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The adrenolytic effect of chlorpromazine has been useful in reversing generalized vasoconstriction in hypovolemic patients.

A biphasic renal response related to changes in arterial pressure and attenuation of renal vasoconstriction have been shown in 12 patients receiving chlorpromazine intravenously in doses of 2.5 to 50 mg. Six patients were normotensive (Group I), three were hypotensive (Group II), and three were in congestive heart failure (Group III). Each patient served as his own control. Changes in arterial pressure, venous pressure, urine flow, creatinine clearance, and sodium excretion were measured. In all patients the immediate drop of 10 to 40 mm. Hg in 1 to 5 minutes in arterial pressure was accompanied by a decrease of 0.05 to 0.37 cc./min. in urinary flow. The arterial pressure returned to control levels within 1 hour but urinary flow increased from 0.03 to 1.45 cc./min. within 15 to 20 min.; this lasted from 1 to 2 hours. Data will be presented showing the increase in urinary flow to be unrelated to glomerular filtration rate and urine sodium excretion to be decreased in Groups I and III by a factor of 30 to 70% and increased in Group II by a factor of 5 to 90%.

It is concluded that Phase I of renal response to chlorpromazine is related to a drop in arterial pressure but that a favorable balance between the pressure and renal vascular resistance (pressure-resistance ratio) is established during Phase II, increasing renal blood flow.

Chlorpromazine is a valuable adjunct to fluid replacement in hypovolemic patients. *(Supported by NIH Postdoctoral Fellowship 1-F2-HE-33393-01.)*

A Study of Factors Determining the Development and Persistence of Atrioventricular Conduction Defects following Ligation of the Anterior Septal Artery

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Previously this laboratory studied atrioventricular conduction in 100 dogs following ligation of the anterior septal artery. It was found that 75% of those dogs surviving the first day after ligation developed arrhythmia and that there was a return to normal sinus rhythm in 67% by the fourth day after ligation. This study was designed to investigate the factors that determine whether an atrioventricular conduction defect will develop and persist after ligation of the anterior septal artery. The artery was ligated

in 50 healthy dogs in which normal sinus rhythm was present postoperatively. Electrocardiograms were monitored daily. After sacrifice at 1, 2, 3, and 4 days after ligation, serial sections taken from the atrioventricular node, bundle of His, right and left bundle branches, and adjacent myocardium were prepared by the standard staining techniques and by frozen sections stained for potassium by a modification of the cobaltinitrite method of Gersh. Of the dogs subjected to the ligation 87% developed arrhythmia; 8% had partial necrosis of the conduction tissue but with a normal potassium milieu, and did not develop arrhythmia; and 5% of ligated dogs developed no infarction and had no arrhythmia. Of the 87% of dogs with arrhythmia, 13% had no necrosis of the conducting tissue itself; 61 had partial necrosis; 13% had an area of total cross-sectional necrosis. Return to normal sinus mechanism in these groups was observed in 40%, 30%, and 0% respectively. Since 87% of ligated dogs were sacrificed before the fourth day postligation when a significant percentage of recovery occurs, total per cent recovery of normal sinus rhythm of 24% was less than the 67% observed previously in this laboratory. The dogs that returned to normal sinus rhythm had a normal potassium milieu at sacrifice. Partial necrosis of the conducting tissue was not sufficient for the development of arrhythmia if the potassium milieu of the remaining viable fibers was normal. When continuity was present in as little as 6.5% of His fibers, a normal sinus mechanism was maintained in a normal potassum milieu. Arrhythmias were observed only if the conducting tissue was in a milieu of increased potassium or if there was total cross-sectional necrosis of an area of the conducting tissue independent of the potassium milieu. There was no correlation between the extent of edema and inflammatory reaction and the presence of conduction disturbances. *(Supported in part by USPHS and AHA.)*

Myocardial Contractility After Elective Ventricular Fibrillation

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Electrically induced ventricular fibrillation is widely used to obtain reversible cardiac arrest during cardiac surgery and has been termed both innocuous and "not without risk" on the basis of data obtained by various investigators from left ventricular function curves. In order to delineate further the effect of ventricular fibrillation on the heart, the effect of one hour of ventricular fibrillation on left ventricular contractility was studied in the isovolumic preparations in dogs. Myocardial contractility curves before and after fibrillation were obtained by plotting known left ventricular balloon volumes against: 1) the left ventricular pressure (LVP), 2) the LVP with paired pulse stimulation of the left ventricle, 3) the maximal rate of left ventricular pressure rise (dP/dT), and 4) the dP/dT with paired pulse stimulation of the left ventricle.

One hour of ventricular fibrillation did not adversely affect the myocardial contractility of the left ventricle as measured by LVP and by dP/dT curves, with or without paired pulse stimulation. In some animals myocardial contractility of the left ventricle was improved after fibrillation as measured by LVP and dP/dT curves without paired pulse stimulation. *(Supported in part by USPHS and AHA.)*

Studies of the Effects of Lidocaine on the Electrical and Mechanical Activity of the Heart

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Lidocaine was found to depress the force of contraction of the isovolumic left ventricle of dogs on complete cardiopulmonary bypass. The degree of inotropic depression was usually dose-related and little depression was found with doses in the therapeutic range (0.5 to 2.0 mg./kg.). Lidocaine also had a negative inotropic action when the heart was paced by paired electircal stimuli, a means of inducing a maximal contractile response from heart muscle.

The drug was found to slow the atrial and ventricular rates of dogs with complete atrioventricular (AV) block. The degree of slowing was dose-related and the effect upon atrial pacemakers was less marked than upon ventricular pacemakers. Using bipolar electrodes it was found that lidocaine in a dose of 5 to 10 mg./kg. slowed conduction from the sinoatrial (SA) node to the bundle of His but had little effect on intra-atrial and intraventricular conduction. Lidocaine also opposed the slowing of the SA node and the delay in AV conduction caused by vagal stimulation.

Lidocaine was given intravenously to 27 patients with atrial and ventricular arrhythmias. The drug was found to be most effective against ectopic ventricular rhythms, especially those related to digitalis excess, and terminated the arrhythmia in 9 of 11 patients. Three of 4 AV nodal arrhythmias were terminated by lidocaine. Only 1 of 8 atrial arrhythmias was controlled by the drug. In the dose employed (0.5 to 4.0 mg./kg. given rapidly intravenously), only 1 patient experienced hypotension; this was transient. Mild disturbances of the central nervous system were often observed with doses of 1.5 mg./kg. Convulsions occurred in 3 patients receiving 3 to 3.5 mg./kg. All neurological disturbances were transient and did not require treatment. (*Supported by Veterans Administration Medical Research funds*).

Renal Hemodynamics During Osmotic Diuresis in Man

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Reduction in GFR and extraction of PAH, which occurs during osmotic diuresis in the dog, has been attributed to redistribution of renal blood flow with increased flow to the medulla. In the present study in man, mannitol infusion (10% mannitol 20 ml./min.) in 15 hydropenic subjects resulted in a 25.0% fall in GFR (C_{IN}), and little change in renal blood flow (Δ RBF = —4.4%) or extraction of PAH (E_{PAH}, control 0.842, mannitol 0.839). Wedged renal vein pressure increased from 19.6 mm.Hg (range 15.0 to 25.7 mm.Hg) during control periods to 39.9 mm.Hg (range 38.0 to 41.5 mm.Hg) during osmotic diuresis in 4 studies. Failure to observe a significant

change in renal blood flow or E_{PAH} makes it unlikely that GFR falls as a result of redistribution of blood flow. Proximal tubular fluid reabsorption is decreased during osmotic diuresis and might be expected to result in increased tubular hydrostatic pressure, thereby reducing net filtration pressure. Gottschalk found that wedged renal vein pressures closely approximate increasing proximal tubular pressures in the rat during diuresis. If this relation obtains in man, the present finding of increased wedged renal vein pressure supports the thesis that reduction in GFR during osmotic diuresis is caused by a decrease in net filtration pressure resulting from increased proximal tubular hydrostatic pressure. *(Supported by USPHS Grant HE 03272-10 and by the New York Heart Association.)*

Effect of Diameter on Contractile Behavior of the Isolated Cat Papillary Muscle Preparation

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The viability of isolated tissue preparations of cardiac muscle used in studies of contraction has been in considerable doubt on the basis of studies of oxygen uptake in these tissues, which suggested limitation of diffusion. We have approached this problem by measuring isometric contractile force in cat papillary muscles of different thicknesses. Developed isometric tension was recorded at optimal muscle length, as determined from the length-tension relation. Records were obtained in normal Tyrode solution, in a calcium-rich (10.8 mM) sodium-poor (99.7 mM) Tyrode medium, and during optimal mechanical potentiation from paired electrical stimulation in normal Tyrode. While developed tension in the control state varied considerably from one preparation to another, it was found to be constant in the calcium-rich, sodium-poor medium for eight muscles having diameters less than 0.4 mm. at optimal length (5.75 ± 0.7 gm./mm.^{2}). Recorded developed tensions in the calcium-rich, sodium-poor medium from eight additional muscles with diameters above this value were considerably less (3.82 ± 1.3 gm./mm.^{2}). These results indicate that contractile behavior of this preparation cannot be adequately quantitated for muscles that exceed a rather small critical diameter. The constancy of contractile tension in the thin muscles, as potentiated in the calcium-rich, sodium-poor medium, adds further support to the view that a contractile maximum is elicited in this medium. Paired pulse stimulation in normal Tyrode potentiates developed tension to a degree closely approximating (85%) the contractile maximum. *(Supported by U.S. Public Health Research Grant HE-05142-07).*

The Lack of Correlation Between Airway Resistance and Uneven Ventilation of the Lung in Bronchial Asthma

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Reversible elevations in Airway Resistance (Ra) have been recognized as one of the basic abnormalities in bronchial asthma. While many investigators have demonstrated that Ra is greatly elevated during accute attacks of bronchospasm, and that there is marked nonuniformity of ventilation present as well, no studies have been reported that relate these two variables. The present investigation was performed to study what effect, if any, decreasing Ra, measured by body plethysmography, would have on the distribution of ventilation measured by nitrogen washout technique.

Six patients under 35 years of age, with histories of episodic attacks of wheezing, and good family and personal histories of allergy, were studied during acute untreated attacks of bronchospasm. They were then restudied at various intervals after treatment. The average Ra was 6.56 cm. H_20/1./sec. with a conductance/thoracic gas volume ratio (GA/TGV) of 0.04/1./sec./cm. H_20/l. After bronchodilators Ra and GA/TGV fell to 2.1 cm H_2/l./sec. and 0.18 l./sec./cm. H_2o/l. respectively. The N_2 washouts, in contrast, changed very little before and after treatment. Five of six patients maintained a three compartment system with the mean ventilation of the slow compartment—total ventilation ratio (VS/VT) falling from 7.6 to 4.1. The ventilatory distribution returned to normal in only one subject.

The results of this study suggest that in bronchial asthma bronchodilator therapy affects the larger airways, but may not significantly influence the areas responsible for the uneven ventilation. *(Supported in part by the USPHS Grant 5TO1 HE 5485-05.)*

Effects of Changes in Arterial Potassium on Myocardial K Balance

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The interpretation of changes in myocardial K balance following an intervention must frequently be made in the presence of changing arterial levels of potassium. This investigation was designed to study the effects of changing arterial K concentration on myocardial K balance. A catheter was placed in the coronary sinus of closed-chest anesthetized dogs under controlled respiration. Automated sampling of arterial and coronary sinus blood was achieved by pumping simultaneously from equal dead space catheters, at identical flow rates, at a rate of one sample (4 ml.) per minute. Equilibrated blood was returned to the dog at the same rate as its removal. Aortic pressure, heart rate and arterial *p*H were steady throughout. A KCl infusion of 0.76 mEq./min. resulted in average maximal coronary A-V differences of 0.63 mEq./l. (control 0.03). The amount of A-V difference appears to be related to the rate of arterial K rise. A fall in arterial K following discontinuation of the infusion was associated with coronary venous K exceeding arterial K by an average of 0.40 mEq./l. These data show that myocardial K balance and presumably myocardial K are affected by arterial concentration changes. This must be considered in the evaluation of factors that may affect myocardial K. *(Supported by USPHS Grant 2621.)*

Correlation of Electrocardiogram Changes with Alterations of the Transmembrane Action Potentials of Single Cardiac Cells in the In Situ *Heart Under Various Experimental Conditions*

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With the introduction of the "flexibly-mounted glass microelectrode with tungsten wire" by Woodbury and Brady, recordings of the transmembrane action potentials of single cardiac cells from the *in situ* heart were attempted by many investigators. Such measurements in vigorously beating hearts were usually limited to less than 10 minutes for a particular microelectrode because of the great fragility of the tip. Moreover, the tungsten wire had the additional disadvantage of being polarizable. To overcome these two drawbacks, we developed a *flexibly mounted nonpolarizing ultraflexible glass microelectrode,* which was connected to the exposed Ag-AgCl-coated end of a Teflon-coated silver wire. With this improved microelectrode system, which combined utmost flexibility with a minimum of polarization, continuous recordings of the transmembrane action potentials of single cardiac cells of vigorously beating hearts could be made for more than one hour in dogs and rabbits and for several hours in rats, turtles and frogs.

Measurements of the transmembrane action potential (TAP) of single cardiac cells were carried out simultaneously with recordings of the ECG in the *in situ* heart and with the arterial blood pressure.

It was found that the rising phase of the TAP of ventricular cardiac cells corresponded to a specific part of the QRS complex and that the end of the TAP corresponded to specific phases of the end of the T-wave or U-wave. The particular positions varied with the location of the cell within the heart. Within one minute after i.v. injection of heparin (200 to 1000 units/kg. body weight) various degrees of shortening of the QT interval of the ECG were observed frequently. This corresponded with shortening of the duration of the TAP of single cardiac cells. The phenomenon usually lasted less than 10 minutes in both rabbits and rats. In rats, these changes were particularly pronounced and were often accompanied by the formation of U-waves. There was a slight decrease in blood pressure but no change in heart rate. With larger doses of heparin (more than 800 units/kg. body weight), transitional WPW Syndrome was observed in some instances.

The intravenous injection of Isoproterenol (0.1μgm.-100 μgm./kgm. body weight) into intact rabbits and rats caused a fall in blood pressure and an increase in heart rate. In open-chest animals, the increase in heart rate did not occur. In fact, raising the dose to more than 200-500 μgm./kgm. usually resulted in a slowing of the heart rate.

Partial crushing of up to 60 to 80% of the anterior wall of right ventricle by a curved clamp usually did not produce any noticeable changes in TAP of the remaining cells of the right or left ventricle and in standard limb lead ECG. When more than 80% of the entire right ventricle was thoroughly crushed without rupturing it, frequently the time duration of TAP of the remaining right ventricular cells as well as of the left ventricular cells was markedly shortened with a noticeable change in ECG. (*Supported by USPHS Grant HE-00890-16.*)

Potassium Shifts After Operation for Acquired Heart Disease

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Many patients with acquired heart disease come to operation with total body potassium (K_E) seriously depleted. Determinations of serum K^+ concentration may or may not reveal this depletion. Serious K^+-responsive arrhythmias have been reported in such patients.

This study was undertaken to determine: *a*) the degree of K^+ depletion preoperatively in a group of patients with acquired heart disease *b*) the amount of K^+ loss during bypass and in the postoperative period *c*) the rate of K^+ restitution postoperatively, and *d*) the effect of a regimen with relatively large amounts of K^+ supplementation in the postoperative period.

The ^{42}K isotope dilution technique was used to measure the preoperative and postoperative K_E in 11 patients. Operative serum K^+ determinations and standard postoperative balance studies of Na^+ and K^+ were undertaken in 16 patients.

Preoperatively the mean K_E of 11 patients was 27.9 ± 6.2 mEq./kg. (66% normal). There was no significant change in the K_E in the early postoperative period despite large amounts of K^+ supplementation. Studies are under way to determine the rate of restitution of K_E.

Serum K^+ always fell during bypass, usually by 0.8-1.0 mEq./l. Balance studies of Na^+ and K^+ in 16 patients revealed uniform retention of Na^+ and net K^+ loss through the 4th day despite a mean K^+ supplementation of $55^{\pm}$ 18 mEq./day for the first 4 postoperative days. The mean cumulative Na^+ retention was $310^{\pm}$ 155 mEq. and the mean cumulative K^+ loss was $108^{\pm}$ 80 mEq. during this period.

With the K^+ replacement regimen, serum K^+ was either relatively unchanged, or increased slightly, despite the net K^+ loss. Patients receiving no K^+ supplementation exhibited a consistent slight fall in serum K^+ and a similar net K^+ loss.

Using this regimen of K^+ therapy only one serious ventricular arrhythmia occurred in a series of 56 patients with acquired valvular disease. The rate of occurrence of supraventricular arrhythmias appeared unaffected. *(Supported by NIH General Research Support Grant FR 05501-04.)*

Nonsurgical Intra-Arterial Cardiac Assistance

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Experimental results with a method of intra-aortic volume displacement are presented. Based on the concept of diastolic balloon pumping described by Moulopoulos *et al.* and Clauss *et al.*, this method promises advantages in the treatment of cardiogenic shock. It can be applied easily and rapidly; blood flows at low velocities and is circulated only intracorporeally; and the displaced blood volume is not limited by the size and condition of the femoral artery.

The device, which is inserted into the aorta through the femoral artery, consists of a tapered, cylindrical, thin-walled poly-

urethane chamber with a siliconized polyethylene catheter and a flexible metal mesh tube inside the chamber; this permits rapid filling and emptying with helium.

During cardiac diastole, filling of the polyurethane chamber with helium displaces an equal volume of blood, resulting in an increase in systemic blood pressure and thus in the blood flow to the coronary arteries.

During systole the stroke volume of the left ventricle displaces the helium in the chamber against a low resistance, with resultant decrease in end-diastolic pressure and in the work of the failing left ventricle.

An electronic controller provides two independent time delays for the onset and termination of the pump cycle, triggered by either the R-wave from the ECG or the ascending slope of the left ventricular pressure curve.

Tests on 30 dogs with the functioning unit showed an average decrease of 20% in tension-time index in normal animals, and an increase of 11% in carotid pressure and 10% in femoral arterial pressure in animals with coronary shock induced by litigation of the descending coronary artery. Mechanical assistance was given for periods varying from 10 minutes to 2 hours. *(This work was supported by USPHS Grant HE-06510.)*

Incorporation of Labeled Amino Acid into Protein by Cultured Human Lymphocytes in Health and Disease

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A method has been developed for studying lymphocyte function in various disease states, including uremia, neoplasia, macroglobulinemia, autoimmune diseases, hyperglobulinemic conditions, transplantation, and others. The technique reproducibly measures incorporation of radioactive amino acid into TCA precipitable counts by human peripheral lymphocytes *in vitro*. The technique in outline is as follows. Erythrocytes are sedimented from heparinized blood with gelatin, neutrophils, adsorbed onto nylon, lymphocytes washed and counted. Lymphocytes are cultured overnight in duplicate at 37° C. in a CO_2 incubator in leucine-free media to which C^{14} leucine is added. After lysing the erythrocytes, cold leucine and protein carrier are added, protein is precipitated with TCA and washed with TCA, acetone, and then counted. Cells are counted from simultaneously grown cultures. When grown in the presence of puromycin, the cells incorporate less than 10% of control cells. Phytohemagglutinin stimulates protein production twenty- to fortyfold.

Uremic lymphocytes have decreased ability to incorporate C^{14} leucine, whereas normal lymphocytes are not inhibited by urea or creatinine in concentrations of up to 300 mg. % and 20 mg. % respectively. There is decreased uptake by idiopathic macroglobulinemic cells and increased uptake by cells from a patient with dermatomyositis. Drugs with known effects on the immune response *in vivo* are being investigated by this method. We are also attempting to identify humoral factors affecting lymphocytes in disease and health. This system offers a novel approach to the study of human disease mechanisms at a cellular as well as a subcellular level. *(Supported by USPHS Grant 68736 and by the New York Heart Association.)*

The Single Injection Technique for Frequent Evaluation of Blood Volume During Experiments not Associated with Blood Loss

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The purpose of this study was to determine the validity of blood volume determinations made at frequent intervals during a 4-hour period following a single injection of radioactive iodinated (I^{131}) human serum albumin (RIHSA). The usual method requires approximately a 1-hour time lapse between determinations and thereby limits the number of determinations that may be made in a given interval of time. Serial blood volume determinations were made with a Picker Hemolitre on 25 dogs under light thiopental sodium anesthesia over a period of 4 hours. In Part I of the study, the apparent blood volume of 10 dogs was plotted against time (with the apparent increase in circulating volume reflecting the disappearance of the RIHSA from the vasculature). The graph that resulted showed that the date of disappearance of the RIHSA could be correlated with the "true" blood volume. In order to check the blood volume in the usual manner, a second injection of RIHSA was given at the end of the 4-hour period; the volume determined was essentially the same as that found at the beginning of the period. In Part II of the study, the graph obtained in Part I was used to calculate the blood volumes at frequent intervals on fifteen additional animals following a single injection of RIHSA. Five of these were identical to those in Part I, five received a dextrose in water infusion, and five received a low molecular weight dextran infusion. At the end of a 4-hour period the calculated blood volumes were compared to a value obtained by the usual method (using a second RIHSA injection) and the difference averaged less than 4%. The data support the conclusion that a single injection of RIHSA allows accurate blood volume determinations to be made at frequent intervals during a 4-hour period in studies not associated with blood loss. *(Supported in part by USPHS and AHA.)*

Effect of Erythrocyte Lipoprotein on the Coagulation Mechanism

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Erythrocyte membrane lipoprotein was prepared from both dog and human red cells after washing, freezing, thawing, and differential ultracentrifugation at 53,000 g in a low ionic strength, *p*H 7.4, citrate-phosphate buffer. Eighteen separate experiments have been performed in dogs anaesthetized with pentothal. Five dogs had sham procedures and were used as controls. Both femoral veins were catheterized; blood was then drawn at 0, 5, 15, 30, 45 minutes and 24 hours. At these times, clot-

ting time, platelet count, one stage prothrombin time, partial thromboplastin time, and chemical fibrinogen level were measured. The other animals, after control samples were obtained, were individually given rapid or slow infusions of whole blood, rapid or slow infusions of RBC lipoprotein into the femoral vein. The total lipid extracted from 150 ml. of whole blood was given rapidly into the femoral vein after first being emulsified with albumin. In another experiment, 180 ml. of whole blood was rapidly infused into the splenic vein of two dogs.

Rapid infusion of whole blood into the peripheral circulation caused death within 3 minutes. Slow infusions did not cause death, but there was marked drop in the platelet count. RBC lipoprotein, in addition to a marked drop in the platelet count, caused shortening of the clotting time. The lipid extract of whole blood and the splenic vein infusions of whole blood did not cause an immediate drop in the platelet count or shorten the clotting time.

Since the platelet counts fell every time the clotting time shortened, it is pertinent to speculate that the erythrocyte lipoprotein may play an important role in the pathogenesis of thrombosis in Sickle Cell Crisis, transfusion reactions, and defibrination syndromes. *(Supported by the John A. Polachek Foundation and Fannie Ripple Foundation.)*

Hemodynamic Studies with a Newly Designed Auxiliary Ventricle in Dogs

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A new form of mechanical auxiliary ventricle has been developed for rapid implantation in the ascending aorta by means of a single incision. It is avalvular and spherical, and contains a small baffle or septum that partly separates the inner pumping chamber so that all the blood can flow through easily and freely with a minimal risk of stagnation. The flexible inner chamber is made of silicone rubber and the outer housing of fiber glass covered with silicone rubber.

The unit is implanted in the ascending aorta during short-term inflow and outflow occlusion of the heart. The time required for the actual insertion and temporary ligation of the two limbs is 2 minutes. After this the circulation is reestablished and the anastomosis completed.

The device is driven by compressed air from an outside tank via a polyethylene air tube. The flow is interrupted by a solenoid valve triggered by either the R-wave from the ECG or the ascending slope of the left ventricular pressure curve.

Experiments on 14 dogs showed that the most favorable hemodynamic effects could be obtained when the auxiliary ventricle was implanted in the ascending aorta as close to the heart as possible. The reduction in tension-time index was found to reach 50% in some cases.

The advantages of this new unit are: 1) it can be implanted in the ascending aorta by means of a single incision, and 2) it can be inserted easily and rapidly (2 minutes). Like the U-shaped auxiliary ventricle, it has no valves, so that blood from the left ventricle can pass through the unit freely—thus the clotting problem is no greater than in any other artificial arterial graft; it can be driven either continuously or intermittently; and it is premanently implanted. *(This work was supported by USPHS Grant HE-06510.)*